

### REMARKS

Claims 14, 15, 17, 18, and 24-27 are now pending. Reconsideration of the application is solicited in view of the following remarks.

#### Finality of the office action

In this office action, the Examiner rejected claim 17 on a new ground, i.e., anticipation by Hickey et al. (WO 97/15325). Since this rejection was not initiated by Applicants' amendment to this claim in response to the previous office action (dated June 5, 2002), it is improper for the Examiner to make this office action final. Thus, Applicants ask the Examiner to reconsider and withdraw the finality of this office action.

#### Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 24-27 as containing new matter. Specifically, the Examiner asserted that there is no support in the specification for a limitation recited in these claims, i.e., "excludes the non-receptor binding domain of the *Pseudomonas* exotoxin A." See the Office Action, page 3, part 11.

Applicants respectfully traverse. According to the paragraph bridging pages 10 and 11 of the specification, plasmid pPEDIG12 contains a DNA sequence encoding the receptor binding domain of *Pseudomonas* exotoxin A and 12 copies of GnRH repeats (PE Ia-GnRH12). Other portions of the PE DNA sequence (i.e., the sequence encoding the non-receptor binding domain) is not included in this construct. Note that, when determining whether a specification is in compliance with the written description requirement, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed, and that the subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement. See MPEP 2163.02. Based on the description of pPEDIG12 in the specification, a skilled artisan would understand that this plasmid excludes the sequence encoding the non-receptor binding domain of PE. Thus, the limitation recited in claims 24-27, "excludes the non-receptor binding domain of the *Pseudomonas* exotoxin A" is not new matter.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 14, 15, 17, and 18 on two grounds, each of which is discussed in detail below:

I

Claims 14 and 18 remain rejected as being anticipated by Lorberboum-Galski et al. (U.S. Patent No. 6,140,066), as evidenced by Burnie et al. (European Application No. 0 406 029 A1). See the Office Action, page 4, part 12.

Claim 14 is drawn to a nucleic acid encoding a polypeptide that contains (1) the receptor binding domain of a *Pseudomonas* exotoxin A, and (2) at least three copies of an antigenic peptide sequence. Claim 18 is drawn to a nucleic acid similar to that of claim 14 except that copies of the antigenic peptide sequence are in a consecutive series.

Lorberboum-Galski et al. discloses a DNA sequence encoding a polypeptide comprising the full-length *Pseudomonas* exotoxin A and one to three copies of a linker sequence of five amino acids, GGGGS. The Examiner asserted that the linker sequence serves as an antigen in view of Lorberboum-Galski et al. and Burnie et al. Thus, the Examiner concluded that, since claims 14 and 18 contain the open-ended language "comprises," they are anticipated by Lorberboum-Galski et al., as the full-length *Pseudomonas* exotoxin A inherently includes the receptor binding domain.

Applicants disagree. It is well known in the art that not every peptide is antigenic. In the case of the linker sequence GGGGS, Lorberboum-Galski et al. states:

"Such linker has been used in constructing single chain antibodies (scFv) by being inserted between  $V_H$  and  $V_L$  ... The linker is designed to enable the correct interaction between two beta-sheets forming the variable region of the single chain antibody." (See column 2, lines 56-65.)

It does not mention that the linker sequence itself is antigenic. To the contrary, as a structural component of the antibody, the linker sequence is usually preferred to be non-antigenic.

Burnie et al., on the other hand, discloses the sequence of a *Candida albicans* stress protein. The paragraph referred to by the Examiner is as follows:

"Particular fragments of a stress protein according to the invention include any peptide epitopes, for example of a few amino acids or analogues thereof.

Examples of such epitopes include STDEPAGESA, LSREM, LKVIRK and LKVIRKNIVKKMIE ..." (emphasis added)

This statement indicates that only particular fragments of the disclosed stress protein, not any peptide (e.g., GGGGS), is antigenic. Note that GGGGS is not even a fragment of the disclosed stress protein.

In sum, Lorberboum-Galski et al., as evidenced by Burnie et al., does not disclose a nucleic acid encoding a PE-containing polypeptide having at least three copies of an antigenic peptide sequence. Therefore, it does not anticipate claim 14 or 18.

## II

The Examiner further rejected claims 14-18 (presumably claims 14, 15, 17, and 18) as being anticipated by Hickey et al. (WO 97/15325). See the Office Action, pages 4 and 5, part 13.

Claims 14 and 18 have been discussed in section (I) above. Claim 15 is drawn to a nucleic acid similar to that of claim 14 except that the antigenic peptide sequence contains SEQ ID NO:1 (i.e., GnRH). Claim 17 is drawn to a nucleic acid similar to that of claim 14 except that the copy number of the antigenic peptide sequence is 10 to 20. All of the nucleic acids of these claims include a sequence encoding at least three copies of an antigenic peptide sequence.

Hickey et al. discloses GnRH-PE conjugates produced by chemical means and GnRH-PE chimeric hybrid proteins produced using recombinant DNA technology. In a GnRH-PE conjugate, GnRH is chemically attached to PE via a linker. In particular, multiple copies of GnRH can be first attached to a scaffold, and the GnRH-scaffold is then attached to PE. In a GnRH-PE chimeric hybrid protein, there may be two tandem repeats of GnRH (see page 9, lines 29-32). The Examiner asserted that claims 14, 15, 17, and 18 are anticipated by Hickey et al. due to the open-ended language "comprises" recited in these claims.

Applicants disagree. As mentioned above, in Hickey et al., GnRH-PE conjugates are produced by chemical means and do not involve any nucleic acid. On the other hand, to produce a GnRH-PE chimeric hybrid protein using recombinant DNA technology, the encoding nucleic acid used in Hickey et al. may include a sequence coding for two tandem repeats of GnRH. There is no teaching in Hickey et al. about a nucleic acid containing a sequence encoding at least

three copies of an antigenic peptide sequence. Thus, Hickey et al. does not anticipate claim 14, 15, 17, or 18, which is drawn to a nucleic acid containing a sequence encoding at least three copies of an antigenic peptide sequence.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 24-27 as being unpatentable over Hickey et al. in view of Hwang et al. (J. Biol. Chem. 264:2379-2384, 1989) and Pastan et al. (U.S. Patent No. 4,892,827). See the Office Action, pages 5-7, part 14. Applicants respectfully traverse.

Claims 24-27 are drawn to nucleic acids including a sequence encoding the receptor binding domain of a *Pseudomonas* exotoxin A and excluding a sequence encoding the non-receptor binding domain of the *Pseudomonas* exotoxin A.

Hickey et al. has been discussed above. Hwang et al. discloses structure/function relationship of *Pseudomonas* exotoxin A. Pastan et al. discloses modified *Pseudomonas* exotoxins with deletions in at least domain Ia.

As correctly pointed out by the Examiner, the nucleic acid sequence disclosed in Hickey et al. encodes the full-length PE protein. The Examiner asserted that (1) Hickey et al. teaches that variant PE DNA sequences can be used in a hybrid construct, (2) Hwang et al. teaches that the Ia domain of PE (i.e., the receptor binding domain) can be used for vaccination purposes, and (3) Pastan et al. teaches hybrid proteins including PE Ia and luteinizing hormones. It is the Examiner's position that it would have been *prima facie* obvious to a skilled artisan to replace the sequence encoding the full-length PE protein taught by Hickey et al. with a sequence encoding the Ia domain of PE taught by Hwang et al. or Pastan et al. The Examiner stated that one would have been motivated to do so, with a reasonable expectation of success, as the Ia domain is a variant of the full-length PE and the Ia domain would provide advantages of reduced toxicity and blocking of toxin binding to cells.

Applicants disagree. The number of PE variants is enormous. A PE variant can be any fragment of PE, any insertion, deletion or substitution mutant of PE, or any chemically modified molecule of PE. None of the three references cited by the Examiner provides a reason why, among the numerous PE variants, domain Ia should be chosen to replace the full-length PE

protein encoded by the nucleic acid disclosed in Hickey et al. Hwang et al. only teaches that the Ia domain of PE itself can be used for producing vaccines against PE-mediated diseases. It does not suggest that the Ia domain can be used as an antigen carrier to facilitate induction of immune responses against the antigen. Further, although PE Ia is less toxic than the full-length PE protein, it appears not to be the choice of Pastan et al., as PE with a deletion of domain Ia exhibits greatly diminished toxicity (see column 6, lines 18-28). Also, in Pastan et al., the “modified *Pseudomonas* exotoxins” fused to peptide hormones refer to PE mutants containing “deletions in at least domain 1A” (see, e.g., Abstract). Moreover, Hickey et al. specifically states that the preferred *Pseudomonas* exotoxin variants are those having decreased toxicity, for example, having amino acids 1-252 (domain Ia) deleted. See, e.g., the paragraph bridging pages 9 and 10. As such, the three references cited by the Examiner, alone or combined, do not provide motivation for a skilled artisan to combine them together in the way suggested by the Examiner. To the contrary, by emphasizing deletion of domain Ia, both Pastan et al. and Hickey et al. teach away from claims 24-27, which are all drawn to nucleic acids including a sequence encoding the receptor binding domain (i.e., the Ia domain) of a *Pseudomonas* exotoxin A.

For the reasons set forth above, Applicants submit that claims 24-27 are patentably distinguishable from the prior art references cited by the Examiner, and the rejection should be withdrawn.

The Examiner also made of record but did not rely on one additional prior art reference: Russell-Jones et al. (WO 91/02799). Applicants have reviewed it and found that it does not render claims 24-27 obvious.

### CONCLUSION

Applicants submit that the grounds for rejection asserted by the Examiner have been overcome, and that claims 14, 15, 17, 18, and 24-27, as pending, define subject matter that is sufficiently described, novel, and nonobvious over the prior art. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.